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1. L6 ANSWER 62 OF 72 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:116525 CAPLUS
DOCUMENT NUMBER: 120:116525
TITLE: Comments on the application of liposome technology to specific cell targeting
AUTHOR(S): Leserman, Lee; Suzuki, Hiroichiro; Machy, Patrick
CORPORATE SOURCE: Cent. Immunol., CNRS, Marseille, Fr.
SOURCE: Liposome Technol. (2nd Ed.) (1993), Volume 3, 139-51. Editor(s): Gregoriadis, Gregory. CRC: Boca Raton, Fla.
CODEN: 59PWAV
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review with 52 refs.

2. ANSWER 64 OF 72 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:154215 CAPLUS
DOCUMENT NUMBER: 118:154215
TITLE: Cell specific liposomes in biotechnology and medicine
AUTHOR(S): Sunamoto, Junzo
CORPORATE SOURCE: Dep. Polym. Chem., Kyoto Univ., Kyoto, 606, Japan
SOURCE: Proc. Int. Symp. Controlled Release Bioact. Mater., 19th (1992), 182-3. Editor(s): Kopecek, Jindrich. Controlled Release Soc.: Deerfield, Ill.
CODEN: 58JTAJ
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review with 8 refs. Receptor-mediate cell uptake, targeting to phagocytes, serum-free culture of fibroblasts, and liposome vaccines are discussed.

Class - NO

3. ANSWER 27 OF 72 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1982:129223 BIOSIS
DOCUMENT NUMBER: PREV198223059215; BR23:59215
TITLE: SPECIFIC LIPOSOME CELL INTERACTIONS.
AUTHOR(S): LESERMAN L D [Reprint author]; BARBET J; MACHY P
CORPORATE SOURCE: CENTRE IMMUNOL INSERM-CNRS MARSEILLE-LUMINY, CASE 906, 13288 MARSEILLE CEDEX 2, FR
SOURCE: Journal of Supramolecular Structure and Cellular Biochemistry, (1981) No. SUPPL. 5, pp. 261.
Meeting Info.: MEETING ON CELLULAR RECOGNITION PRESENTED AT THE ICN-UNIVERSITY OF CALIFORNIA AT LOS ANGELES SYMPOSIA ON MOLECULAR AND CELLULAR BIOLOGY, MARCH 1-7, 1981. J SUPRAMOL STRUCT CELL BIOCHEM.
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Cell Specific Liposomes in Biotechnology and Medicine

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Introduction

Since 1982, we have developped several methodologies to achieve receptor-mediated cell uptake of liposomes. These methods involve (1) reconstitution of a cell recognizable glycoprotein in liposome, (2) coating of the outermost surface of liposome with a cell specific polysaccharide derivative, and (3) conjugation of monoclonal antibody subunit to polysaccharide derivative and coating of liposome with it. Recently, importance of the receptor specific saccharides has been revealed. In this paper, the preparation of cell specific liposomes and the receptor-mediated cell uptake of these modified liposomes will be introduced relating with several applications in biotechnology and medicine, such as serum free cell culture of fibrobrast, treatment of canser diseases in animals, immunomodulation of macrophages, vaccination against ATL and Balb RVD leukemia in animals, and so forth.

Receptor-mediated cell uptake

In order to obtain more information about the relationship between the cell-specificity and the chemical structure of terminal sugar moiety of the polysaccharides for coating liposome, we newly synthesized several pullulan derivatives which in part carry galactosamine, 1-aminogalactose, mannosamine, 1-aminomannose, glucosamine, 1-aminoglucose, sialic acid, 1-aminolactose, or 1-aminoserobiose. First of all, specific lectin-induced aggregation of the liposome coated with these pullulan derivatives was investigated. As the result, extent of the lectin-induced aggregation of polysaccharide-coated liposome was closely correlated with the specificity of the terminal saccharide moiety on the liposomal surface to the lectin employed. Secondly, the internalization efficiency of these polysaccharide-coated liposomes was examined for phagocytes (alveolar macrophages of guinea pig, human neutrophils and monocytes, and Kupffer cells), liver parenchymal cell, fibrobrast, and several tumor cells. The cell uptake of the polysaccharide-coated liposome was able to be effectively controlled by altering only the terminal sugar residue of the polysaccharides. The polysaccharide-coated liposomes seem to be useful probe for searching unknown receptor of various cells.

Targeting to phagocytes

One difficulty in practical use of liposomes as drug carrier is that liposomes are rapidly entrapped by the macrophages in reticuloendothelial system (RES). However, such a feature of liposome is not disadvantage for the delivery of drugs such as immunomodulator or interferon inducer to macrophages. In order to more effectively modulate the *in vivo* (adjuvant) activity of an immunopotentiator, we attempted the encapsulation of several immunomodulators into a macrophage-specific liposome as coated with the mannan-cholesterol derivatives and obtained several successful results. This methodology was attempted to treat several infectious diseases in animals.

Serum free culture of fibrobrast

In order to make liposome targetable to fibroblast, partly phosphorylated mannan was synthesized, and egg phosphatidylcholine liposome was coated by phosphorylated mannan so

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obtained. The specific interaction between the phosphorylated mannan-coated liposome and mouse fibroblast (L-cell) was certainly observed. The medium, which contains the modified liposome loading several water-soluble and insoluble nutrients, was superior for serum free culture of mouse fibroblasts.

Liposomal vaccines

Most important process for the enhancement of immunogenicity by endogeneous antigen is effective internalization of the antigen into antigen presenting cells. The adjuvant activity of liposome for inducing effective humoral and cellular immune responses has been demontrated in several systems. It has been demonstrated in several cases, meantime, that immunoprotection to grafted tumor and/or viral infection is achieved by the production of MHC class I restricted CD^{8+} cytotoxic T lymphocytes (CTL). *In vivo* immunization of WKA/H rats was tried with the use of a polysaccharide-coated liposome bearing a HTLV-1 related protein, *gag-env* hybrid protein. The *gag-env* hybrid protein-reconstituted liposome was prepared by coincubation of eggPC-DDPC liposome with the *gag-env* hybrid protein. By the protein-reconstituted liposomes with or without polysaccharide coat, WKA/H rats were subcutaneously immunized. Effective prevention against HTLV-1 was observed only by the case as immunized with the CHM-coated *gag-env*-reconstituted liposome.

Conclusion

Information obtained was very useful not only in the development of cell specific materials but also in the understanding of the role of saccharides in intercellular communications.

References

1) Cell Specificity of Polysaccharide Derivatives on Liposomal Surface, K. Akiyoshi, H. Takanabe, T. Sato, T. Sato. H. Kondo, and J. Sunamoto, Chem. Lett., 473-476 (1990).

2) Targeting Chemotherapy of Brain Tumor Using Liposome-Encapsulated Cisplatin-Part 2. Pullulan-Coated Liposomes to Target Brain Tumor, A. Ochi, S. Shibata, K. Mori, T. Sato, and J. Sunamoto, D.D.S.,*5*, 261-265 (1990).

3) Priming for *In vitro* and *In vivo* Anti HTLV-1 Cellular Immunity by Virus Related Protein Reconstituted into Liposome, Y. Noguchi, T. Noguchi, T. Sato, Y. Yokoo, S. Itoh, M. Yoshida, T. Yoshiki, K. Akiyoshi, J. Sunamoto, E. Nakayama, and H. Shiku, J. Immunol. 146, 3599 (1991).

4) Induction of *in vitro* and *in vivo* Anti-Tumor Responses by Sensitization of Mice with Liposomes Containing a Crude Butanol Extract of Leukemia Cells and Transferred Intermembranously with Cell Surface Proteins, R. Shibata, T. Noguchi, T. Sato, K. Akiyoshi, J. Sunamoto, H. Shiku, and E. Nakayama, Int. Journal of Cancer, (1991).

5) Direct Transfer of Tumor Surface Antigenic Protein (TSAP) from Tumor Cell to Liposome for Making Liposomal Vaccine, J. Sunamoto, T. Noguchi, T. Sato, K. Akiyoshi, R. Shibata, E. Nakayama, and H. Shiku, J. Controlled Release, (1992) in press.

6) Polysaccharides for Pharmaceutical and Medical Applications Drug Delivery Systems, J. Sunamoto, in "Cellulosics Utilization", ed. by H. Inagaki, and G.O. Phillips, Elsevier Applied Science, 246-254 (1989).

7).Improved Drug Delivery Directed to Specific Tissue Using Polysaccharide-coated Liposomes, J. Sunamoto and T. Sato, in "Multi. Bio. Mat.", ed by T. Tsuruta and A. Nakajima, VSP, 167-190 (1989).

8) Cell Specific Drug Release from Liposomes, J. Sunamoto, K. Akiyoshi, and T. Sato, in "Topics in Pharmaceutical Sciences", Amsterdam Medical Press, Noordwijk, The Netherlands, 25-38 (1989).